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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/282,239	03/31/1999	STEVEN A. GOLDMAN	19603/1426	8339

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EXAMINER
HUTSON, RICHARD G

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1652	24

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Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No. 09/282,239	Applicant(s) GOLDMAN ET AL.	
	Examiner Richard G Hutson	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19 and 21-26* is/are pending in the application.

4a) Of the above claim(s) *24-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants cancellation of claims 1-18 and 20, amendment of claim 19 and addition of new claims 21-26 is acknowledged. Applicants filing of a declaration under 1.132, Paper No. 20, 6/10/2002, is also acknowledged. Claims 19 and 21-26 are at issue and are present for examination.

Newly submitted claims 24-26 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 24-26 drawn to a method of treating a subject with a demyelinating disease. These claims are related to the elected group as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the currently elected product can be used in materially different processes such as methods of study of precursor and stem cell biology.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 24-26 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Applicants' arguments filed on 6/10/2002, paper No. 18, have been fully considered and are deemed to be persuasive to overcome some of the rejections

previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 23 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Newly added claim 23 is indefinite in that it is unclear what applicants consider to be the metes and bounds of the phrase "substantially pure" when referring to the progenitor cells of the claimed invention. While one of skill in the art generally would understand this term, it is not clear at what point a preparation is and is not considered "substantially pure".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 19 and 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Armstrong et al. (Journal of Neuroscience 12 (4): 1538-1547, April 1992).

This rejection is stated in the previous office action, Paper No. 9, 12/5/2000, traversed in , Paper No. 12, 6/11/2001, and maintained for previous claims 17 and 18 in Paper No. 13, 8/27/2001, The original rejection is repeated below for applicants convenience.

Armstrong et al. teach the existence and preparation of preparations enriched in human postnatal oligodendrocytes and oligodendrocyte progenitor cells. Specifically Armstrong et al. characterize the glial cell population of adult human white matter after culturing in defined medium for 1-2 weeks (see Results pages 1540-1541 and Figure 2). Armstrong teach cultures which are enriched and substantially pure for both oligodendrocytes and pre-oligodendrocytes cells (See Figures 1-3 and supporting text on pages 1539-1542). Thus, Armstrong et al. anticipate claims 17-20 to an enriched or purified preparation of human postnatal oligodendrocytes or oligodendrocytes progenitor cells.

Claims 19 and 21-23 are currently drawn to an enriched or purified preparation of human mitotic oligodendrocyte progenitor cells, wherein said cells are from a post-natal (Claim 21) or adult (Claim 22) human and wherein the cells are substantially pure (Claim 23). It is acknowledged that claims to the same subject matter were previously

withdrawn from this rejection, but after further consideration of applicants response to this earlier rejection has resulted in the claims to this subject matter being added back to the rejection.

Applicants traversed this rejection on the basis that the pre-oligodendrocytes of Armstrong and the oligodendrocytes they produce did not undergo cell division (i.e. mitosis) when treated with mitosis-triggering agents, and thus it is clear that these cells are not mitotic, as was recognized by Armstrong et al. and this is in contrast to the oligodendrocyte progenitor cells of the present invention. Thus since Armstrong et al. does not teach mitotic oligodendrocyte progenitor cells it cannot be used as a proper basis to reject the claims.

Applicants earlier traversal that the cells isolated by Armstrong et al. are not mitiotic, is not found persuasive on the following basis. Armstrong et al., specifically teach the preparation comprising "fresh human temporal lobe obtained from biopsies of patients undergoing therapeutic resection for intractable epilepsey which had menginges, blood vessels and the majority of gray matter removed from before mincing" (See page 1539 under *Glial Cell Isolation*) constitutes an "enriched or purified preparation". While it is acknowledged that Armstrong et al. did not identify pre-oligodendrocytes nor oligodendrocytes which incorporated ^{3}H-thymidine in response to certain specific stimuli, the preparation taught by Armstrong et al. does comprise human mitotic oligodendrocyte progenitor cells and their presence is an inherent property of the "enriched or purified preparation" taught by Armstrong et al. The basis of the presence of the mitotically active human oligodendrocyte progenitor cells in the preparation of

Armstrong et al. is a similar preparation as was used by applicants to further isolate the claimed mitotically active human oligodendrocyte progenitor cells. Specifically, on page 16 of the instant specification, applicants teach that the claimed mitotically active human oligodendrocyte progenitor cells were isolated from adult human brain tissues obtained from lobectomy of epilepsey patients.

Claims 19 and 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Kirschenbaum et al. (Cerebral Cortex 6: 576-589, Nov/Dec 1994).

This rejection is stated in the previous office action, Paper No. 9, 12/5/2000, traversed in , Paper No. 12, 6/11/2001. The original rejection is repeated below for applicants convenience.

Kirschenbaum et al. teach that cells derived from the subependymal zone (SZ) and periventricular white matter of the adult human forebrain can indeed generate and differentiate into neurons in culture. Kirschenbaum et al. teach the culturing of adult human temporal lobe tissue samples in a defined medium for 7-28 days at which point the cell populations were characterized by immunocytochemistry, ^{3}H-thymidine labeling, calcium imaging and cellular morphology. Specifically Kirschenbaum et al. teach that subcortical white matter cultures are enriched in $O4^{+}$ oligodendrocytes and fiborous astrocytes (See page 581, *Subcortical Phenotypes*), while the SZ comprises precursors that embarked upon neural differentiation (See page 584, *Source of the Neuronal Precursor Cells* and page 585, right column, second paragraph). Thus, Kirschenbaum

et al. anticipate claims 17 and 21-23 to an enriched or purified preparation of human postnatal oligodendrocytes or oligodendrocytes progenitor cells.

Applicants continue to traverse this rejection on the basis that Kirschenbaum et al. does not disclose mitotic oligodendrocyte progenitor cells, thus the rejection should be withdrawn. Applicants position is further supported by the declaration of Dr. Goldman, Paper No. 20.

Applicants submit a recitation from page 582 of Kirschenbaum et al. from which applicants conclude that all of the oligodendrocytes were post-mitotic. In response to this specifically recited passage, applicants attention is directed to the recitation which directly follows the above passage which states"... In contrast, a second comparatively uncommon category of $O4^+$ cells was characterized by a larger (15-25 mm), flatter, and more substrate-apposed soma; each cell projected several relatively thick, long and tapering, unbranched processes. These cells constituted <1% of the $O4^+$ population, and frequently incorporated ^{3}H-thymidine. The onotogeny and fate of these $O4^+/^3$H-thymidine+ cells are now being evaluated separately..." This second passage clearly teaches that the preparation of Kirschenbaum et al. did comprise a substantially pure mitotically active O4+ cell population, albeit a small population.

Irregardless of whether or not Kirschenbaum et al. teach the presence of mitotically active human oligodendrocytes progenitor cells in the taught preparations, as discussed above, with respect to the preparation of Armstrong et al., Kirschenbaum et al. teach a preparation comprising "adult human temporal lobe obtained during anterior temporal lobectomy of epilepsey patients followed by dissociation for single-cell

monolayer culture (See page 577 under *Tissue Samples* and *Culture preparation*) which constitutes an "enriched or purified preparation". While it is acknowledged that Kirschenbaum et al. did not identify pre-oligodendrocytes nor oligodendrocytes which incorporated ^{3}H-thymidine *in vitro* in response to certain specific stimuli, the preparation taught by Kirschenbaum et al. does comprise human mitotic oligodendrocyte progenitor cells and their presence is an inherent property of the "enriched or purified preparation" taught by Kirschenbaum et al. The basis of the presence of the mitotically active human oligodendrocyte progenitor cells in the preparation of Kirschenbaum et al. is that this preparation is similar to that preparation used by applicants to further isolate the claimed mitotically active human oligodendrocyte progenitor cells. Specifically, on page 16 of the instant specification, applicants teach that the claimed mitotically active human oligodendrocyte progenitor cells were isolated from adult human brain tissues obtained from lobectomy of epilepsey patients.

The rejection of claims 17 and 19 under 35 U.S.C. 102(b) as being anticipated by Bottenstein (U.S. Patent No: 5,276,145, January 1994) has been withdrawn on the basis of applicants cancellation of claim 17 and applicants amendment of claim 19 to being drawn to **human** mitotic oligodendrocyte progenitor cells.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 19, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bottenstein (U.S. Patent No: 5,276,145, January 1994).

As discussed previously and repeated here for applicants convenience, Bottenstein teach compositions comprising a purified preparation of neural progenitor regulatory factor and methods of its use. Bottenstein specifically teach the preparation and characterization of neonatal rat brain cultures (Table I, columns 12-16). Bottenstein specifically teach additional morphological and antigenic characterization of there cultures (Column 23, lines 47-68). After 4 days in vitro cultures treated with 33% B104 conditioned medium contain abundant numbers of small A2B5-positive, bipolar glial progenitor cells which appear to be highly mitotic. These cells give rise to oligodendrocytes.

One of ordinary skill in the art would be motivated to use the composition and methods of isolating and culturing rat mitotic glial progenitor cells to isolate and culture human mitotic glial progenitor cells for their use in the development of a rational therapeutic regime for treatment of demyelinating disorders such as multiple sclerosis or treatment of traumatic injury to the CNS. The reasonable expectation of success of achieving an enriched or purified preparation of glial progenitor cells (oligodendrocyte progenitor cells) comes from the results of Bottenstein and the similarity of the different cell types between rat and human brains.

Applicants traverse this rejection as Bottenstein was previously applied as 102 art and applicants support there position by submitting a declaration under 1.132 by Dr Steven Goldman.

Applicants submit that Bottenstein is directed to substantially purified preparations of a neural progenitor regulatory factor isolated from a mixture of cell types that included "progenitors as well as other cell types (Goldman Declaration, paragraph 6). Applicant is reminded that a cell preparation comprising a mixture of cell types as discussed above would still anticipate an enriched or purified preparation of any cell found in the preparation.

Applicants submit that there are fundamental differences between the biology of rat and human oligodendrocyte progenitor cells, which are not addressed in Bottenstein which discusses findings limited to the neonatal rat brain. Specifically applicants assert that that while the rat oligodendrocytes appear to retain mitotic potential, human oligodendrocytes do not (Applicants point to Kirschenbaum et al.) (Goldman Declaration, paragraph 7). For this reason applicants assert that the oligodendrocyte progenitor cell of the rat brain cannot be considered homologous to its human counterpart. Applicants further submit that Bottenstein was directed to the enrichment of glial cells from newborn rat brain (Goldman Declaration, paragraph 8) and that newborns have an abundant population of still-developing oligodendrocyte progenitor cells.

Applicants further point out that in contrast to the cells acquired from the newborn rats using the Bottenstein protocol, the present invention is achieved with a protocol that

permits the selective extraction and purification of progenitor cells biased to the oligodendrocyte phenotype from tissues in which they are scarce, thus this resulted in a far greater enrichment than the procedure of Bottenstein (Goldman Declaration, paragraphs 9 and 10). While this argument as supported in the Goldman declaration is acknowledged applicant is reminded that the currently rejected claims are directed to merely an enriched or purified preparation of mitotically active human oligodendrocyte progenitor cells and that the claims to this subject matter do not include any of the differences in purity of the progenitor cell preparation which applicants assert.

Finally applicants conclude for the reasons discussed above, and supported in the Goldman declaration, that the selective propagation of mitotically –active oligodendrocyte progenitor cells from the neonatal rat brain, as thought by Bottenstein, does not predict the successful isolation of mitotic oligodendrocyte progenitor cells from postnatal or adult human brain tissue. While as discussed above and acknowledged, the protocol taught by Bottenstein does not result in a preparation of mitotically active oligodendrocyte progenitor cells with a purity as great as that of the instant application, irregardless, applicant is reminded that such a "pure" preparation is not necessary to anticipate the rejected claims as they are merely drawn to an **enriched or purified** preparation of human mitotically active oligodendrocyte progenitor cells.

Thus claims 19 and 21-23 are made obvious by Bottenstein.

Claims 19 and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldman et al. (U.S. Patent No: 6,245,564 B1, filed January 23, 1997).

Goldman et al. teach a method of separating and a single mammalian oligodendrocyte progenitor cell comprising selecting a promoter which functions only in said cell, introducing a nucleic acid which encodes a fluorescent protein (GFP) under control of said promoter, allowing the cell population to express said fluorescent protein and isolating the substantially pure fluorescent cells from the mixed population. Goldman et al. further teach that there is a strong need for a strategy for isolating and enriching native neuronal precursors and neural stem cells from adult brain tissue for use in engraftment and transplantation. Goldman et al. teach the preparation of precursors from adult human brain, specifically from the adult human temporal ventricular zone (VZ). Goldman et al. further teach that useful GFP constructs based upon early oligodendrocyte promoters such as CNPase may permit the enrichment of oligodendrocyte as well as neuronal precursors from the VZ.

One of ordinary skill in the art at the time of invention would have been motivated to use the methods taught by Goldman et al. to isolate an enriched or purified preparation of human mitotically active oligodendrocyte progenitor cells, for use in engraftment and transplantation protocols. The reasonable expectation of success comes from the results of Goldman et al. who successfully teach methods of enriching and purifying preparations of mitotically active oligodendrocyte progenitor cells and used similar methods to isolate enrich both chick and rat brain neural precursors.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapy Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.
August 26, 2002